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(54) Title: ANTIBIOTIC PRODUCT, USE AND FORMULATION THEREOF

(57) Abstract: An antibiotic product is comprised of at least three delayed release dosages forms, each of which has a different release profile, with the  $C_{max}$  for the antibiotic product being reached in less than about twelve hours.

## **ANTIBIOTIC PRODUCT, USE AND FORMULATION THEREOF**

This invention relates to an antibiotic product, as well as the use and formulation thereof.

A wide variety of antibiotics have been used, and will be used, in order to combat bacterial infection. In general, such antibiotics can be administered by a repeated dosing of immediate release dosage forms, which results in poor compliance or as a controlled release formulation (slow release) at higher administered doses. The present invention is directed to providing for an improved antibiotic product.

In accordance with one aspect of the present invention, there is provided an antibiotic pharmaceutical product which is comprised of at least two, preferably at least three, delayed release antibiotic dosage forms. Such dosage forms are formulated so that each of the delayed release dosage forms has a different release profile.

In a particularly preferred embodiment, there are at least two, preferably at least three delayed release dosage forms, each of which has a different release profile and the release profile of each of the delayed release dosage forms is such that the delayed release dosage forms each start release of the antibiotic contained therein at different

times after administration of the antibiotic product. The antibiotic product in a preferred embodiment does not include an immediate release dosage form.

Thus, in accordance with an aspect of the present invention, there is provided a single or unitary antibiotic product that has contained therein at least two, preferably at least three delayed release antibiotic dosage forms, each of which has a different release profile, whereby the antibiotic contained in each of such dosage forms is released at different times.

In accordance with a further aspect of the invention, the antibiotic product may be comprised of at least four different delayed release dosage forms, each of which starts to release the antibiotic contained therein at different times after administration of the antibiotic product.

The antibiotic product generally does not include more than five delayed release dosage forms with different release times.

In accordance with a preferred embodiment, the antibiotic product has an overall release profile such that when administered the maximum serum concentration of the total antibiotic released from the product is reached in less than twelve hours after initial release of antibiotic from the delayed release dosage form that first releases the antibiotic product, preferably in less than eleven hours. In an embodiment, the maximum serum concentration of the total antibiotic released from the antibiotic product is achieved no earlier than four hours after initial release of antibiotic from the delayed release dosage form that first releases the antibiotic product.

In one embodiment, the second of the at least three delayed release dosage forms initiates release of the antibiotic contained therein at least one hour after the first dosage form, with the initiation of the release therefrom generally occurring no more than six

hours after initiation of release of antibiotic from the first delayed release dosage form of the at least three delayed release dosage forms.

As hereinabove indicated, the antibiotic product may contain at least three or at least four or more different delayed release dosage forms. For example, the antibiotic released from the third dosage form reaches a  $C_{\max}$  at a time later than the  $C_{\max}$  is achieved for antibiotic released from each of the first and second dosage forms. In a preferred embodiment, release of antibiotic from the third dosage form is started after initiation of release of antibiotic from both the first dosage form and the second dosage form. In one embodiment,  $C_{\max}$  for antibiotic release from the third dosage form is achieved within ten hours; however, the  $C_{\max}$  may be achieved in shorter or longer times, provided that the last released dosage form provides a  $C_{\max}$  within twelve hours after initial release from the first dosage form.

In another embodiment, the antibiotic product contains at least four dosage forms, with each of the at least four dosage forms having different delayed release profiles, whereby antibiotic released from each of the at least four different dosage forms achieves a  $C_{\max}$  at a different time.

As hereinabove indicated, in a preferred embodiment, irrespective of whether the antibiotic contains at least three or at least four different delayed release dosage forms each with a different release profile,  $C_{\max}$  for all the antibiotic released from the antibiotic product is achieved in less than twelve hours, and more generally is achieved in less than eleven hours, in each case after initial release of the antibiotic from the first dosage form that releases antibiotic first.

In a preferred embodiment, the antibiotic product is a once a day product, whereby after administration of the antibiotic product, no further product is administered during the day; i.e., the preferred regimen is that the product is administered only once over a twenty-four hour period. Thus, in accordance with the present invention, there is a single administration of an antibiotic product with the antibiotic being released in a

manner such that overall antibiotic release is effected with different release profiles in a manner such that the overall  $C_{\max}$  for the antibiotic product is reached in less than twelve hours after antibiotic is initially released from the product. The term single administration means that the total antibiotic administered over a twenty-four hour period is administered at the same time, which can be a single tablet or capsule or two or more thereof, provided that they are administered at essentially the same time.

Applicant has found that a single dosage antibiotic product comprised of at least three delayed release antibiotic dosage forms each having a different release profile is an improvement over a single dosage antibiotic product comprised of an antibiotic dosage form having a single release profile. Each of the dosage forms of antibiotic in a pharmaceutically acceptable carrier may have one or more antibiotics and each of the dosage forms may have the same antibiotic or different antibiotics.

It is to be understood that when it is disclosed herein that a dosage form initiates release after another dosage form, such terminology means that the dosage form is designed and is intended to produce such later initiated release. It is known in the art, however, notwithstanding such design and intent, some "leakage" of antibiotic may occur. Such "leakage" is not "release" as used herein.

If at least four dosage forms are used, the fourth of the at least four dosage form may be a sustained release dosage form or a delayed release dosage form. If the fourth dosage form is a sustained release dosage form, even though  $C_{\max}$  of the fourth dosage form of the at least four dosage forms is reached after the  $C_{\max}$  of each of the other dosage forms is reached, antibiotic release from such fourth dosage form may be initiated prior to or after release from the second or third dosage form.

The antibiotic product of the present invention, as hereinabove described, may be formulated for administration by a variety of routes of administration. For example, the antibiotic product may be formulated in a way that is suitable for topical administration; administration in the eye or the ear; rectal or vaginal administration; as nose drops; by

inhalation; as an injectable; or for oral administration. In a preferred embodiment, the antibiotic product is formulated in a manner such that it is suitable for oral administration.

For example, in formulating the antibiotic product for topical administration, such as by application to the skin, the different dosage forms, each of which contains an antibiotic, may be formulated for topical administration by including such dosage forms in an oil-in-water emulsion, or a water-in-oil emulsion. For example, there may be provided an oil-in-water-in-oil emulsion, with oil being a continuous phase that contains the one delayed release component, water dispersed in the oil containing a second delayed release dosage form, and oil dispersed in the water containing a third delayed release dosage form.

It is also within the scope of the invention to provide an antibiotic product in the form of a patch, which includes antibiotic dosage forms having different release profiles, as hereinabove described.

In addition, the antibiotic product may be formulated for use in the eye or ear or nose, for example, as a liquid emulsion. For example, the dosage form may be coated with a hydrophobic polymer whereby a dosage form is in the oil phase of the emulsion, and a dosage form may be coated with hydrophilic polymer, whereby a dosage form is in the water phase of the emulsion.

Furthermore, the antibiotic product with at least three different dosage forms with different release profiles may be formulated for rectal or vaginal administration, as known in the art. This may take the form of a cream or emulsion, or other dissolvable dosage form similar to those used for topical administration.

As a further embodiment, the antibiotic product may be formulated for use in inhalation therapy by coating the particles and micronizing the particles for inhalation.

In a preferred embodiment, the antibiotic product is formulated in a manner suitable for oral administration. Thus, for example, for oral administration, each of the dosage forms may be used as a pellet or a particle, with a pellet or particle then being formed into a unitary pharmaceutical product, for example, in a capsule, or embedded in a tablet, or suspended in a liquid for oral administration.

Alternatively, in formulating an oral delivery system, each of the dosage forms of the product may be formulated as a tablet, with each of the tablets being put into a capsule to produce a unitary antibiotic product. Thus, for example, antibiotic products may include three or more additional tablets, each of which provides for a delayed release of the antibiotic, as hereinabove described, whereby the  $C_{\max}$  of the antibiotic released from each of the tablets is reached at different times, with the  $C_{\max}$  of the total antibiotic released from the antibiotic product being achieved in less than twelve hours after initial release of antibiotic.

The formulation of an antibiotic product including at least three dosage forms with different release profiles for different routes of administration is deemed to be within the skill of the art from the teachings herein. As known in the art, with respect to delayed release, the time of release can be controlled by the concentration of antibiotics in the coating and/or the thickness of the coating.

In formulating an antibiotic product in accordance with the invention, in one embodiment, the first delayed release dosage form of the product generally provides from about 20% to about 50% of the total dosage of antibiotic to be delivered by the product, with such first delayed release dosage form generally providing at least 25% of the total dosage of the antibiotic to be delivered by the product. In many cases, the first delayed release dosage form provides from about 20% to about 30% of the total dosage of antibiotic to be delivered by the product; however, in some cases it may be desirable to have the first delayed release dosage form provide for about 45% to about 50% of the total dosage of antibiotic to be delivered by the product.

The remaining dosage forms deliver the remainder of the antibiotic. If more than one delayed release dosage form is used, in one embodiment, each of the delayed release dosage forms may provide about equal amounts of antibiotic; however, they may also be formulated so as to provide different amounts.

In accordance with a preferred embodiment of the present invention, each of the dosage forms contains the same antibiotic; however, each of the dosage forms may contain more than one antibiotic.

In one embodiment, where the composition contains three delayed release components, the first delayed release component provides from 20% to 35% (preferably 20% to 30%), by weight, of the total antibiotic; where there are four delayed release components, the first delayed release component provides from 15% to 30%, by weight, of the total antibiotic; and where there are five delayed release components, the first delayed release component provides from 10% to 25%, by weight, of the total antibiotic.

With respect to the delayed release components after the first delayed release component, where there are three delayed release components, the second delayed release component (the one released earlier in time) provides from 30% to 60%, by weight, of the total antibiotic provided by the two remaining delayed release components with the third delayed release component providing the remainder of the antibiotic.

Where there are four delayed release components, the delayed released component after the first delayed release component provides 20% to 35% by weight of the total antibiotic provided by the four delayed release components, the next in time delayed release component provides from 20% to 40%, by weight, of the antibiotic provided by the four delayed release components and the last in time providing the remainder of the antibiotic provided by the four delayed release components.

When there are five delayed release components, the earliest delayed release component after the first delayed release component provides from 15% to 30%, by

weight, the next in time delayed release component provides from 15% to 30%, the next in time delayed release component provides from 20% to 35%, by weight, and the last in time delayed release component provides from 20% to 35%, by weight, in each case of the total antibiotic provided by the four delayed release components.

The overall composition includes each of the antibiotics in a therapeutically effective amount. The specific amount(s) is dependant on the antibiotic used, the disease or infection to be treated, and the number of times of day that the composition is to be administered.

The antibiotic composition of the present invention may be administered for example, by any one of the following routes of administration: sublingual, transmucosal, transdermal, parenteral, oral, preferably by oral administration.

#### **The Immediate Release Component**

An immediate release component may be initially produced and then coated to produce the delayed release dosage forms used in the present invention.

The immediate release portion of this system can be a mixture of ingredients that breaks down quickly after administration to release the antibiotic. This can take the form of either a discrete pellet or granule that is mixed in with, or compressed with, the other three components.

The materials to be added to the antibiotics for the immediate release component can be, but are not limited to, microcrystalline cellulose, corn starch, pregelatinized starch, potato starch, rice starch, sodium carboxymethyl starch, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, ethylcellulose, chitosan, hydroxychitosan, hydroxymethylatedchitosan, cross-linked chitosan, cross-linked hydroxymethyl chitosan, maltodextrin, mannitol, sorbitol, dextrose, maltose, fructose, glucose, levulose, sucrose, polyvinylpyrrolidone (PVP), acrylic acid derivatives

(Carbopol, Eudragit, etc.), polyethylene glycols, such a low molecular weight PEGs (PEG2000-10000) and high molecular weight PEGs (Polyox) with molecular weights above 20,000 daltons.

It may be useful to have these materials present in the range of 1.0 to 60% (W/W).

In addition, it may be useful to have other ingredients in this system to aid in the dissolution of the drug, or the breakdown of the component after ingestion or administration. These ingredients can be surfactants, such as sodium lauryl sulfate, sodium monoglycerate, sorbitan monooleate, sorbitan monooleate, polyoxyethylene sorbitan monooleate, glyceryl monostearate, glyceryl monooleate, glyceryl monobutyrate, one of the non-ionic surfactants such as the Pluronic line of surfactants, or any other material with surface active properties, or any combination of the above.

These materials may be present in the rate of 0.05-15% (W/W).

#### **The non-pH Sensitive Delayed Release Component**

The components in this composition are the same immediate release unit, but with additional polymers integrated into the composition, or as coatings over the pellet or granule.

Materials that can be used to obtain a delay in release suitable for this component of the invention can be, but are not limited to, polyethylene glycol (PEG) with molecular weight above 4,000 daltons (Carbowax, Polyox), waxes such as white wax or bees wax, paraffin, acrylic acid derivatives (Eudragit), propylene glycol, and ethylcellulose.

Typically these materials can be present in the range of 0.5-25% (W/W) of this component.

**The pH Sensitive (Enteric) Release Component**

The components in this composition are the same as the immediate release component, but with additional polymers integrated into the composition, or as coatings over the pellet or granule.

The kind of materials useful for this purpose can be, but are not limited to, cellulose acetate phthalate, Eudragit L, and other phthalate salts of cellulose derivatives.

These materials can be present in concentrations from 4-20% (W/W).

**Sustained Release Component**

The components in this composition are the same as the immediate release component, but with additional polymers integrated into the composition, or as coatings over the pellet or granule.

The kind of materials useful for this purpose can be, but are not limited to, ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, carboxymethylcellulose, methylcellulose, nitrocellulose, Eudragit R, and Eudragit RL, Carbopol, or polyethylene glycols with molecular weights in excess of 8,000 daltons.

These materials can be present in concentrations from 4-20% (W/W).

As hereinabove indicated, the units comprising the antibiotic composition of the present invention can be in the form of discrete pellets or particles contained in the capsule, or particles embedded in a tablet or suspended in a liquid suspension.

The antibiotic composition of the present invention may be administered, for example, by any of the following routes of administration: sublingual, transmucosal,

transdermal, parenteral, etc., and preferably is administered orally. The composition includes a therapeutically effective amount of the antibiotic, which amount will vary with the antibiotic to be used, the disease or infection to be treated, and the number of times that the composition is to be delivered in a day. The composition is administered to a host in an amount effective for treating a bacterial infection.

This system will be especially useful in extending the practical therapeutic activity for antibiotics with elimination half-lives of less than 20 hours and more particularly with elimination half-lives of less than 12 hours, and will be particularly useful for those drugs with half-lives of 2-10 hours. The following are examples of some antibiotics with half-lives of about 1 to 12 hours: Cefadroxil, cefazolin, cephalixin, cephalothin, cephapirin, cephalor, cephprozil, cephradine, cefamandole, cefonicid, ceforanide, cefuroxime, cefixime, cefoperazone, cefotaxime, cefpodoxime, ceftaxidime, ceftibuten, ceftizoxime, ceftriaxone, cefepime, cefmetazole, cefotetan, cefoxitin, loracarbef, imipenem, erythromycin (and erythromycin salts such as estolate, ethylsuccinate, gluceptate, lactobionate, stearate), azithromycin, clarithromycin, dirithromycin, troleanomycin, penicillin V, penicillin salts, and complexes, methicillin, nafcillin, oxacillin, cloxacillin, dicloxacillin, amoxicillin, amoxicillin and clavulanate potassium, ampicillin, bacampicillin, carbenicillin indanyl sodium (and other salts of carbenicillin) mezlocillin, piperacillin, piperacillin and tazobactam, ticarcillin, ticarcillin and clavulanate potassium, clindamycin, vancomycin, novobiocin, aminosalicylic acid, capreomycin, cycloserine, ethambutol HCl and other salts, ethionamide, and isoniazid, ciprofloxacin, levofloxacin, lomefloxacin, nalidixic acid, norfloxacin, ofloxacin, sparfloxacin, sulfacycline, sulfamerazine, sulfamethazine, sulfamethoxazole, sulfasalazine, sulfisoxazole, sulfapyridine, sulfadiazine, sulfamethoxazole, sulfapyridine, metronidazole, methenamine, fosfomycin, nitrofurantoin, trimethoprim, clofazimine, co-triamoxazole, pentamidine, and trimetrexate.

The invention will be further described with respect to the following examples; however, the scope of the invention is not limited thereby. All percentages in this specification, unless otherwise specified, are by weight.

**non-pH Sensitive Delayed Release Component**

Formulate the composition by mixing the ingredients in a suitable pharmaceutical mixer or granulator such as a planetary mixer, high-shear granulator, fluid bed granulator, or extruder, in the presence of water or other solvent, or in a hot melt process. If water or other solvent was used, dry the blend in a suitable pharmaceutical drier, such as a vacuum oven or forced-air oven. Allow the product to cool, the product may be sieved or granulated, and compressed using a suitable tablet press, such as a rotary tablet press.

	<u>Ingredient</u>	<u>Conc. (% W/W)</u>
Example 1:	Amoxicillin	65% (W/W)
	Microcrystalline cellulose	20
	Polyox	7.5
	Croscarmellose sodium	7.5
Example 2:	Amoxicillin	55% (W/W)
	Microcrystalline cellulose	25
	Polyox	10
	Glyceryl monooleate	10
Example 3:	Amoxicillin	75% (W/W)
	Polyox	10
	Hydroxypropylcellulose	5
	Croscarmellose sodium	10
Example 4:	Clarithromycin	65% (W/W)
	Microcrystalline cellulose	20
	Polyox	7.5
	Croscarmellose sodium	7.5
Example 5:	Clarithromycin	55% (W/W)
	Microcrystalline cellulose	25
	Polyox	10
	Glyceryl monooleate	10
Example 6:	Clarithromycin	75% (W/W)
	Polyox	10
	Hydroxypropylcellulose	5
	Croscarmellose sodium	10

Example 7:	Ciprofloxacin	65% (W/W)
	Microcrystalline cellulose	20
	Polyox	7.5
	Croscarmellose sodium	7.5
Example 8:	Ciprofloxacin	55% (W/W)
	Microcrystalline cellulose	25
	Polyox	10
	Glyceryl monooleate	10
Example 9:	Ciprofloxacin	75% (W/W)
	Polyox	10
	Hydroxypropylcellulose	5
	Croscarmellose sodium	10
Example 10:	Ciprofloxacin	65% (W/W)
	Microcrystalline cellulose	20
	Polyox	7.5
	Croscarmellose sodium	7.5
Example 11:	Ciprofloxacin	55% (W/W)
	Microcrystalline cellulose	25
	Polyox	10
	Glyceryl monooleate	10
Example 12:	Ciprofloxacin	75% (W/W)
	Polyox	10
	Hydroxypropylcellulose	5
	Croscarmellose sodium	10

### Enteric Release Component

Formulate the ingredients by mixing the ingredients in a suitable pharmaceutical mixer or granulator such as a planetary mixer, high-shear granulator, fluid bed granulator, or extruder, in the presence of water or other solvent, or in a hot melt process. If water or other solvent was used, dry the blend in a suitable pharmaceutical drier, such as a vacuum oven or forced-air oven. Allow the product to cool, the product may be sieved or granulated, and compressed using a suitable tablet press, such as a rotary tablet press.

<u>Ingredient</u>	<u>Conc. (% W/W)</u>
-------------------	----------------------

## Example 13:

Amoxicillin	65% (W/W)
Microcrystalline cellulose	20
Cellulose Acetate Pthalate	15

## Example 14:

Amoxicillin	55% (W/W)
Microcrystalline cellulose	25
Cellulose Acetate Pthalate	10
Hydroxypropylmethylcellulose	10

## Example 15:

Amoxicillin	65% (W/W)
Polyox	20
Hydroxypropylcellulose pthalate	10
Eudragit L30D	5

## Example 16:

Amoxicillin	40% (W/W)
Microcrystalline Cellulose	40
Cellulose Acetate Pthalate	10

## Example 17:

Clarithromycin	70% (W/W)
Hydroxypropylcellulose pthalate	15
Croscarmellose sodium	10

## Example 18:

Clarithromycin	75% (W/W)
Polyethylene glycol 2000	10
Eudragit E 30D	15

## Example 19:

Clarithromycin	40% (W/W)
Lactose	50
Eudragit L 30D	10

## Example 20:

Ciprofloxacin	65% (W/W)
Microcrystalline Cellulose	20
Eudragit L 30D	10

## Example 21:

Ciprofloxacin	75% (W/W)
Microcrystalline Cellulose	15

	Hydroxypropylcellulose pthalate	10
Example 22:		
	Ciprofloxacin	80% (W/W)
	Lactose	10
	Eudragit L 30D	10
Example 23:		
	Ciprofloxacin	70% (W/W)
	Polyethylene glycol 4000	20
	Cellulose acetate pthalate	10
Example 24:		
	Ceftibuten	60% (W/W)
	Polyethylene glycol 2000	10
	Lactose	20
	Eudragit L 30D	10
Example 25:		
	Ceftibuten	70% (W/W)
	Microcrystalline cellulose	20
	Cellulose acetate pthalate	10

### Sustained Release Component

Formulate the composition by mixing the ingredients in a suitable pharmaceutical mixer or granulator such as a planetary mixer, high-shear granulator, fluid bed granulator, or extruder, in the presence of water or other solvent, or in a hot melt process. If water or other solvent was used, dry the blend in a suitable pharmaceutical drier, such as a vacuum oven or forced-air oven. Allow the product to cool, the product may be sieved or granulated, and compressed using a suitable tablet press, such as a rotary tablet press.

	<u>Ingredient</u>	<u>Conc. (% W/W)</u>
Example 26:		
	Amoxicillin	65% (W/W)
	Ethylcellulose	20
	Polyox	10
	Hydroxypropylmethylcellulose	5

## Example 27:

Amoxicillin	55% (W/W)
Lactose	25
Polyox	10
Glyceryl monooleate	10

## Example 28:

Amoxicillin	70% (W/W)
Polyox	20
Hydroxypropylcellulose	10

## Example 29:

Clarithromycin	75% (W/W)
Lactose	15
Hydroxypropylcellulose	5
Ethylcellulose	5

## Example 30:

Clarithromycin	75% (W/W)
Polyethylene glycol 4000	10
Lactose	10
Eudragit RL 30D	5

## Example 31:

Clarithromycin	80% (W/W)
Polyethylene glycol 8000	10
Hydroxypropylmethylcellulose	5
Eudragit RS 30D	5

## Example 32:

Ciprofloxacin	75% (W/W)
Hydroxyethylcellulose	10
Polyethylene glycol 4000	10
Hydroxypropylcellulose	5

## Example 33:

Ciprofloxacin	75% (W/W)
Lactose	10
Povidone (PVP)	10
Polyethylene glycol 2000	5

## Example 34:

Ceftibuten	75% (W/W)
Polyethylene glycol 4000	10
Povidone (PVP)	10
Hydroxypropylcellulose	5

**Example 35:**

Ceftibuten	75% (W/W)
Lactose	15
Polyethylene glycol 4000	5
Polyvinylpyrrolidone	5

**All delayed release three pulses****Example 36****Antibiotic Pellet Formulation and Preparation Procedure****Pellet Formulations**

The composition of the Antibiotic pellets provided in Table 1.

**Table 1 Composition of Antibiotic Pellets**

Component	Percentage (%)
Antibiotic drug	92
Avicel PH 101	6.0
Polyoxyl 35 Castor Oil*	1.0
Hydroxypropyl methylcellulose, NF*	1.0
Purified Water	**
Total	100

\*Hydroxypropyl methylcellulose and Cremaphor EL were added as a 2.9% w/w aqueous solution during wet massing.

\*\*Removed during processing

Preparation Procedure for Antibiotic Pellets

- Blend Antibiotic and Avicel® PH 101 using a high shear mixer.
- Add the hydroxypropyl methylcellulose and Polyoxyl 35 Castor Oil binder solution slowly into the powder blend under continuous mixing.
- Extrude the wet mass using an LCI Bench Top Granulator. The diameter of the screen of the Bench Top Granulator is 0.8 mm.
- Spheronize the extrudate using a QJ-230 Spheronizer using a small cross section plate.
- Dry the spheronized pellets at 60°C using a fluid bed dryer until the exhaust temperature reaches 40°C.
- Pellets between 20 and 40 Mesh were collected for further processing.

**Antibiotic Pulse One Pellet Formulation and Preparation Procedure****Preparation of an AQOAT AS-LF Aqueous Coating Dispersion****Dispersion Formulation**

The composition of the aqueous AQOAT AS-LF aqueous coating dispersion applied to the Antibiotic pellets is provided below in Table 2.

**Table 2 AQOAT AS-LF Aqueous Coating Dispersion**

Component	Percentage (%)
AQOAT AS-LF	7.0
Triethyl Citrate	2.0
Talc	2.1
Sodium lauryl sulfate	0.2
Purified Water*	88.7
Solid Content	11.3
Polymer Content	7.0

\*Removed during processing

**Preparation Procedure for an AQOAT AS-LF Aqueous Dispersion**

- Add triethyl citrate (TEC) to the purified water with stirring.
- Add the sodium lauryl sulfate (SLS) to the TEC dispersion with stirring and completely until completely dissolved.
- Add the AQOAT to the TEC/SLS dispersion and stir for at least 30 minutes.

- Add the talc to the AQOAT dispersion and until completely mixed and for at least 30 minutes.
- Screen the dispersion through a No. 60 mesh sieve prior to coating.
- Continue to stir the dispersion until the coating process is complete.

Coating Conditions for the Application of AQOAT AS-LF Aqueous Coating Dispersion

The following coating parameters were used for coating of the AQOAT AS-LF film coating dispersion.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	300 gram
Inlet Air Temperature	48 °C
Outlet Air Temperature	27 °C
Atomization Air Pressure	1.6 Bar
Pump Rate	3-4 gram per minute

Coat Antibiotic pellets with AQOAT AS-LF film coating dispersion such that you apply 30% coat weight gain to the pellets.

**Antibiotic Pulse Two Pellet Formulation and Preparation Procedure****Preparation of an AQOAT AS-HF Aqueous Coating Dispersion****Dispersion Formulation**

The composition of the aqueous AQOAT AS-HF aqueous coating dispersion applied to the Antibiotic pellets is provided below in Table 3.

**Table 3 AQOAT AS-HF Aqueous Coating Dispersion**

Component	Percentage (%)
AQOAT AS-HF	7.0
Triethyl Citrate	2.0
Talc	2.1
Sodium lauryl sulfate	0.2
Purified Water*	88.7
Solid Content	11.3
Polymer Content	7.0

\*Removed during processing

**Preparation Procedure for an AQOAT AS-HF Aqueous Dispersion**

- Add triethyl citrate (TEC) to the purified water with stirring.
- Add the sodium lauryl sulfate (SLS) to the TEC dispersion with stirring and completely until completely dissolved.
- Add the AQOAT to the TEC/SLS dispersion and stir for at least 30 minutes.

- Add the talc to the AQOAT dispersion and until completely mixed and for at least 30 minutes.
- Screen the dispersion through a No. 60 mesh sieve prior to coating.
- Continue to stir the dispersion until the coating process is complete.

Coating Conditions for the Application of AQOAT AS-HF Aqueous Coating Dispersion

The following coating parameters were used for coating of the AQOAT AS-HF film coating dispersion.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	300 gram
Inlet Air Temperature	48 °C
Outlet Air Temperature	27 °C
Atomization Air Pressure	1.6 Bar
Pump Rate	3-4 gram per minute

Coat Antibiotic pellets with AQOAT AS-HF film coating dispersion such that you apply 30% coat weight gain to the pellets.

**Antibiotic Pulse Three Pellet Formulation and Preparation Procedure****Preparation of an Eudragit® FS 30D Aqueous Coating Dispersion****Dispersion Formulation**

The composition of the aqueous Eudragit® FS 30D dispersion applied to the Antibiotic pellets is provided below in Table 4.

**Table 4 Eudragit® FS 30D Aqueous Coating Dispersion**

Component	Percentage (%)
Eudragit® FS 30D	54.8
Triethyl Citrate	0.9
Talc	3.3
Purified Water*	41.0
Solid Content	20.6
Polymer Content	16.4

\*Removed during processing

**Preparation Procedure for an Eudragit® FS 30D Aqueous Dispersion**

- Disperse triethyl citrate (TEC) in the purified water.
- Add the talc in the triethyl citrate dispersion.
- Homogenize the dispersion using a homogenizer.
- Add slowly the Eudragit® FS 30D dispersion to the talc/TEC dispersion with stirring.

Continue to stir the coating dispersion until the coating process is complete.

Coating Conditions for the Application of Eudragit FS30D Aqueous Coating Dispersion

The following coating parameters were used for coating with each of the Eudragit® FS 30 D aqueous film coating.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.2 mm
Material Charge	300 gram
Inlet Air Temperature	38 °C
Outlet Air Temperature	22 °C
Atomization Air Pressure	1.6 Bar
Pump Rate	6 gram per minute

Coat pellets with Eudragit FS 30D coating dispersion dispersion such that you apply 30% coat weight gain to the pellets.

**Antibiotic Tablets**Tableting of the Antibiotic Pellets**Table 5 Composition of Antibiotic Tablets**

Component	Percentage (%)
Silicified microcrystalline cellulose	21.6
Lactose monohydrate	13.0
Povidone	5.0
Pulse One Pellets	18.3
Pulse Two Pellets	18.3
Pulse Three Pellets	18.3

Croscarmellose sodium	5.0
Magnesium stearate	0.5
Total	100

- Blend the silicified microcrystalline cellulose, lactose monohydrate, povidone, colloidal silicon dioxide and Antibiotic coated pellets for 15 minutes in a tumble blender.
- Add the magnesium stearate to the blender, and blend for 5 minutes.
- Compress the blend on a rotary tablet press.
- The fill weight should be adjusted to achieve the desired dose.

#### **Encapsulation of the Antibiotic Pellets**

Pellets are filled into hard gelatin capsules at a ratio of 33.4%: 33.3%: 33.3%: Pulse One, Pulse Two, and Pulse Three Pellets respectively. The capsule is filled with the three different pellets to achieve the desired dose.

The present invention is particularly advantageous in that there is provided an antibiotic product which provides an improvement over twice a day administration of the antibiotic and an improvement over a once a day administration of the antibiotic.

Numerous modification and variations of the present invention are possible in light of the above teachings and therefore, within the scope of the appended claims the invention may be practiced otherwise than as particularly described.

#### **All delayed release four pulses**

##### **Example 37**

#### **Antibiotic Pellet Formulation and Preparation Procedure**

##### Pellet Formulations

The composition of the Antibiotic pellets provided in Table 6.

**Table 6 Composition of Antibiotic Pellets**

Component	Percentage (%)
Antibiotic drug	92
Avicel PH 101	6.0
Polyoxyl 35 Castor Oil*	1.0
Hydroxypropyl methylcellulose, NF*	1.0
Purified Water	**
Total	100

\*Hydroxypropyl methylcellulose and Cremaphor EL

were added as a 2.9% w/w aqueous solution during wet massing.

\*\*Removed during processing

#### Preparation Procedure for Antibiotic Pellets

- Blend Antibiotic and Avicel® PH 101 using a high shear mixer.
- Add the hydroxypropyl methylcellulose and Polyoxyl 35 Castor Oil binder solution slowly into the powder blend under continuous mixing.
- Extrude the wet mass using an LCI Bench Top Granulator. The diameter of the screen of the Bench Top Granulator is 0.8 mm.
- Spheronize the extrudate using a QJ-230 Spheronizer using a small cross section plate.
- Dry the spheronized pellets at 60°C using a fluid bed dryer until the exhaust temperature reaches 40°C.
- Pellets between 20 and 40 Mesh were collected for further processing.

**Antibiotic Pulse One Pellet Formulation and Preparation Procedure****Preparation of an AQOAT AS-LF Aqueous Coating Dispersion****Dispersion Formulation**

The composition of the aqueous AQOAT AS-LF aqueous coating dispersion applied to the Antibiotic pellets is provided below in Table 7.

**Table 7 AQOAT AS-LF Aqueous Coating Dispersion**

Component	Percentage (%)
AQOAT AS-LF	7.0
Triethyl Citrate	2.0
Talc	2.1
Sodium lauryl sulfate	0.2
Purified Water*	88.7
Solid Content	11.3
Polymer Content	7.0

\*Removed during processing

**Preparation Procedure for an AQOAT AS-LF Aqueous Dispersion**

- Add triethyl citrate (TEC) to the purified water with stirring.
- Add the sodium lauryl sulfate (SLS) to the TEC dispersion with stirring and completely until completely dissolved.
- Add the AQOAT to the TEC/SLS dispersion and stir for at least 30 minutes.

- Add the talc to the AQOAT dispersion and until completely mixed and for at least 30 minutes.
- Screen the dispersion through a No. 60 mesh sieve prior to coating.
- Continue to stir the dispersion until the coating process is complete.

Coating Conditions for the Application of AQOAT AS-LF Aqueous Coating Dispersion

The following coating parameters were used for coating of the AQOAT AS-LF film coating dispersion.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	300 gram
Inlet Air Temperature	48 °C
Outlet Air Temperature	27 °C
Atomization Air Pressure	1.6 Bar
Pump Rate	3-4 gram per minute

Coat Antibiotic pellets with AQOAT AS-LF film coating dispersion such that you apply 30% coat weight gain to the pellets.

**Antibiotic Pulse Two Pellet Formulation and Preparation Procedure****Preparation of an Eudragit® L 30 D-55 Aqueous Coating Dispersion****Dispersion Formulation**

The composition of the aqueous Eudragit L30D-55 aqueous coating dispersion applied to the Antibiotic pellets is provided below in Table 8.

**Table 8 Eudragit® L 30 D-55 Aqueous Coating Dispersion**

Component	Percentage (%)
Eudragit® L 30D-55	44.4
Triethyl Citrate	1.3
Talc	6.7
Purified Water*	47.6
Solid Content	21.3
Polymer Content	13.3

\*Removed during processing

**Preparation Procedure for an Eudragit® L 30D-55 Aqueous Dispersion**

- Disperse triethyl citrate (TEC) in the purified water.
- Add the talc into the triethyl citrate dispersion.
- Homogenize the dispersion using a homogenizer.
- Add the TEC/talc dispersion to Eudragit L30D-55 latex dispersion and stir for at least 30 minutes.
- Screen the dispersion through a No. 60 mesh sieve prior to coating.

- Continue to stir the dispersion until the coating process is complete.

Coating Conditions for the Application of Eudragit L30D-55 Aqueous CoatingDispersion

The following coating parameters were used for coating of the Eudragit® L 30 D-55 film coating dispersion.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	300 gram
Inlet Air Temperature	45 °C
Outlet Air Temperature	32 to 35 °C
Atomization Air Pressure	1.6 Bar
Pump Rate	3-4 gram per minute

Coat Antibiotic pellets with Eudragit L30 D-55 film coating dispersion such that you apply 30% coat weight gain to the pellets.

**Antibiotic Pulse Three Pellets Formulation and Preparation Procedure****Preparation of an AQOAT AS-HF Aqueous Coating Dispersion****Dispersion Formulation**

The composition of the aqueous AQOAT AS-HF aqueous coating dispersion applied to the Antibiotic pellets is provided below in Table 9.

**Table 9 AQOAT AS-HF Aqueous Coating Dispersion**

Component	Percentage (%)
AQOAT AS-HF	7.0
Triethyl Citrate	2.0
Talc	2.1
Sodium lauryl sulfate	0.2
Purified Water*	88.7
Solid Content	11.3
Polymer Content	7.0

\*Removed during processing

**Preparation Procedure for an AQOAT AS-HF Aqueous Dispersion**

- Add triethyl citrate (TEC) to the purified water with stirring.
- Add the sodium lauryl sulfate (SLS) to the TEC dispersion with stirring and completely until completely dissolved.
- Add the AQOAT to the TEC/SLS dispersion and stir for at least 30 minutes.

- Add the talc to the AQOAT dispersion and until completely mixed and for at least 30 minutes.
- Screen the dispersion through a No. 60 mesh sieve prior to coating.
- Continue to stir the dispersion until the coating process is complete.

Coating Conditions for the Application of AQOAT AS-HF Aqueous Coating Dispersion

The following coating parameters were used for coating of the AQOAT AS-HF film coating dispersion.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	300 gram
Inlet Air Temperature	48 °C
Outlet Air Temperature	27 °C
Atomization Air Pressure	1.6 Bar
Pump Rate	3-4 gram per minute

Coat Antibiotic pellets with AQOAT AS-HF film coating dispersion such that you apply 30% coat weight gain to the pellets.

**Antibiotic Pulse Four Pellet Formulation and Preparation Procedure****Preparation of an Eudragit® FS 30D Aqueous Coating Dispersion****Dispersion Formulation**

The composition of the aqueous Eudragit® FS 30D dispersion applied to the Antibiotic pellets is provided below in Table 10.

**Table 10 Eudragit® FS 30D Aqueous Coating Dispersion**

Component	Percentage (%)
Eudragit® FS 30D	54.8
Triethyl Citrate	0.9
Talc	3.3
Purified Water*	41.0
Solid Content	20.6
Polymer Content	16.4

\*Removed during processing

**Preparation Procedure for an Eudragit® FS 30D Aqueous Dispersion**

- Disperse triethyl citrate (TEC) in the purified water.
- Add the talc in the triethyl citrate dispersion.
- Homogenize the dispersion using a homogenizer.
- Add slowly the Eudragit® FS 30D dispersion to the talc/TEC dispersion with stirring.

Continue to stir the coating dispersion until the coating process is complete.

Coating Conditions for the Application of Eudragit FS30D Aqueous Coating Dispersion

The following coating parameters were used for coating with each of the Eudragit® FS 30 D aqueous film coating.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.2 mm
Material Charge	300 gram
Inlet Air Temperature	38 °C
Outlet Air Temperature	22 °C
Atomization Air Pressure	1.6 Bar
Pump Rate	6 gram per minute

Coat pellets with Eudragit FS 30D coating dispersion dispersion such that you apply 30% coat weight gain to the pellets.

**Antibiotic Tablets**Tableting of the Antibiotic Pellets**Table 11 Composition of Antibiotic Tablets**

Component	Percentage (%)
Silicified microcrystalline cellulose	21.5
Lactose monohydrate	13.0
Povidone	5.0
Pulse One Pellets	13.75
Pulse Two Pellets	13.75
Pulse Three Pellets	13.75

Pulse Four Pellets	13.75
Croscarmellose sodium	5.0
Magnesium stearate	0.5
Total	100

- Blend the silicified microcrystalline cellulose, lactose monohydrate, povidone, colloidal silicon dioxide and Antibiotic coated pellets for 15 minutes in a tumble blender.
- Add the magnesium stearate to the blender, and blend for 5 minutes.
- Compress the blend on a rotary tablet press.
- The fill weight should be adjusted to achieve the desired dose.

#### **Encapsulation of the Antibiotic Pellets**

Pellets are filled into hard gelatin capsules at a ratio of 25%: 25%: 25%: 25% Pulse One, Pulse Two, Pulse Three and Pulse Four Pellets respectively. The capsule is filled with the four different pellets to achieve the desired dose.

The present invention is particularly advantageous in that there is provided an antibiotic product which provides an improvement over twice a day administration of the antibiotic and an improvement over a once a day administration of the antibiotic.

Numerous modification and variations of the present invention are possible in light of the above teachings and therefore, within the scope of the appended claims the invention may be practiced otherwise than as particularly described.

## WHAT IS CLAIMED IS:

1. An antibiotic product comprising: a first delayed release antibiotic dosage form, a second delayed release antibiotic dosage form, and a third delayed release antibiotic dosage form, each of said first, second and third delayed release antibiotic dosage forms comprising an antibiotic and a pharmaceutically acceptable carrier, said three dosage forms having different release profiles, said antibiotic product reaching a  $C_{max}$  in less than about twelve hours, said antibiotic product being free of an immediate release dosage form.
2. The product of Claim 1 wherein the  $C_{max}$  for the product is reached no earlier than four hours after administration.
3. The product of Claim 2 wherein the product is an oral dosage form.
4. The product of Claim 3 wherein the antibiotic released from the second dosage in the form reaches a  $C_{max}$  in the serum after  $C_{max}$  is reached in the serum for antibiotic released from the first dosage form.
5. The product of Claim 4 wherein the antibiotic released from the third dosage form reaches a  $C_{max}$  in the serum after the antibiotic released from the second dosage form reaches a  $C_{max}$  in the serum.
6. The antibiotic product of Claim 1 wherein said antibiotic product includes a total dosage of antibiotic that is effective for a twenty four hour period.
7. The product of Claim 1 and further comprising a fourth antibiotic dosage form comprising an antibiotic and a pharmaceutically acceptable carrier, wherein antibiotic released from the fourth dosage form reaches a  $C_{max}$  in the serum after  $C_{max}$  is achieved in the serum for antibiotic released from each of the first, second and third dosage forms.
8. A process for treating a bacterial infection in a host comprising:  
administering to a host the antibiotic product of Claim 1.
9. A process for treating a bacterial infection in a host comprising:  
administering to a host the antibiotic product of Claim 2.
10. A process for treating a bacterial infection in a host comprising:  
administering to a host the antibiotic product of Claim 3.
11. A process for treating a bacterial infection in a host comprising:

- administering to a host the antibiotic product of Claim 4.
12. A process for treating a bacterial infection in a host comprising:  
administering to a host the antibiotic product of Claim 5.
13. A process for treating a bacterial infection in a host comprising:  
administering to a host the antibiotic product of Claim 6.
14. A process for treating a bacterial infection in a host comprising:  
administering to a host the antibiotic product of Claim 7.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/24186

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : A61K 9/00, 9/20, 9/22, 9/14, 9/54

US CL : 424/400, 464, 468, 472, 457, 458, 484; 514/964

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/400, 464, 468, 472, 457, 458, 484; 514/964

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Continuation Sheet

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,794,001 A (MEHTA et al) 27 December 1988 (27.12.1988), column 4, examples, and figures.	1-14
Y	WO 98/22091 A1 (YISSUM RESEARCH DEVELOPMENT CO.) 28 May 1998 (28.05.1998), abstract.	1-14

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

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**INTERNATIONAL SEARCH REPORT**

PCT/US03/24186

**Continuation of B. FIELDS SEARCHED Item 3:**

WEST, MEDLINE, STN

search terms: pulsatile release, delayed release, antibiotics, Cmax